Advisory Committee Briefing Document

ABT-414 for the Treatment of Pediatric Patients with High-Grade Gliomas

AbbVie Inc.

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee

Meeting Date: November 19, 2015

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List of Abbreviations and Definitions of Terms

AMD	Abbott Molecular Diagnostics
AUC	Area under the concentration-time curve
C_{max}	Maximum observed plasma concentration
CYP	Cytochrome P450
EGFR	Epidermal growth factor receptor
EGFRvIII	Epidermal growth factor receptor mutant de2-7
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EU	European Union
FISH	Fluorescent in situ hybridization
GBM	Glioblastoma multiforme
HGG	High-grade glioma
IND	Investigational New Drug
ITCC	Innovative Therapies for Children with Cancer
mAb	Monoclonal antibody
mc	Maleimidocaproyl
MMAF	Monomethylauristatin F
NCCN	National Comprehensive Cancer Network
PDX	Patient-derived xenograft
RANO	Revised Assessment in Neuro-Oncology
RTOG	Radiation Therapy Oncology Group
SPECTA	Screening Patients for Efficient Clinical Trial Access
TMZ	Temozolomide
US	United States
WHO	World Health Organization

Executive Summary

High-grade glioma (HGG), defined as Grade III or IV glioma, has no adequate therapy and is almost universally fatal in both the adult and pediatric populations. Approximately 7% of the reported brain and central nervous system tumors occur in children aged 0 to 19 years. Pediatric HGG is a rare tumor with an annual incidence of approximately 0.85/100,000 persons/year. The incidence rates for glioblastoma multiforme (GBM), the most aggressive type of glioma, in the United States during 2004 through 2008 were 0.09 (0 to 4 years old), 0.14 (5 to 9 years old), 0.15 (10 to 14 years old), and 0.18 (15 to 19 years old) per 100,000 person-years.

Despite many attempts to improve upon the available treatment options for patients with HGG, there remains an urgent unmet need in this population because it has no adequate therapy and is almost universally fatal.

To address the unmet medical need for a GBM treatment, AbbVie Inc. (AbbVie) is developing ABT-414, an antibody-drug conjugate comprised of the humanized chimeric anti-epidermal growth factor receptor (EGFR) monoclonal antibody ABT-806 conjugated via a stable maleimidocaproyl linker to a potent tubulin inhibitor, monomethylauristatin F. It is designed to bind to an epitope that is available predominantly on tumor cells with EGFR mutant de2-7 or activated wild-type EGFR.

In the adult population, approximately 40% of all GBM tumors are found to have EGFR gene amplification. However, the EGFR amplification rate is 0% to 5% in pediatric patients with HGG.

ABT-414 is being studied in 5 ongoing studies in adults with GBM, and AbbVie has received orphan drug designation for ABT-414 for GBM in the United States and glioma in the European Union. Preliminary efficacy data on response rates and duration of response are encouraging in patients with GBM with EGFR-amplified tumors. Based on the current efficacy data and emerging safety profile of ABT-414, global Phase 2 studies have been initiated in both newly diagnosed and recurrent EGFR-amplified GBM.

AbbVie has also begun discussions with potential pediatric investigators regarding the potential for studying ABT-414 in pediatric patients with HGG. However, with approximately 0.85 cases of pediatric HGG per 100,000 persons/year and EGFR amplification rates less than 5%, identifying enough children to conduct a standalone pediatric study with even modest objectives would take many years to complete. Therefore, to address the operational feasibility associated with recruiting pediatric patients, AbbVie is planning for a large screening and recruitment that would allow for inclusion of pediatric patients with EGFR-amplified HGGs as a nested cohort within a current ongoing adult study (EORTC BTG-1410/M14-483). The primary objective of the nested cohort would be the assessment of the safety and pharmacokinetics of ABT-414 in these pediatric patients. While the patient numbers may be small, AbbVie believes this approach offers the best chance of identifying, recruiting, and studying ABT-414 in a pediatric population with a rare fatal disease and limited treatment options.

1.0 Disease Background

1.1 Overview of Glioblastoma Multiforme in Adults

Adult high-grade glioma (HGG) includes both Grade III (anaplastic astrocytoma) and Grade IV (glioblastoma multiforme [GBM]) gliomas. Glioblastoma multiforme, the highest grade glioma (Grade IV) and most malignant form of astrocytoma, is also the most common and most aggressive primary brain tumor in adults, accounting for 15.6% of all primary malignant and nonmalignant brain and central nervous system tumors, and 54.4% of all gliomas.[1] Glioblastoma multiforme can occur in patients of any age, but it is more common in adults, with the median age at diagnosis of 64 years.[1,2]

Adult GBM tumors have a high rate of epidermal growth factor receptor (EGFR) gene amplification (approximately 40% of all GBM tumors), which is highly associated with EGFR protein overexpression.[3] Approximately 50% of tumors with EGFR amplifications also express the most common variant of EGFR, an 801 bp in-frame deletion that removes exons 2 through 7 and is referred to as EGFR mutant de2-7 (EGFRvIII).[4] Common dysregulation of EGFR in GBM among adult patients makes it well suited for an EGFR-directed antibody-drug conjugate.

The current standard of care therapeutic regimen for newly diagnosed GBM includes surgical resection, radiotherapy in combination with temozolomide (TMZ), and TMZ as adjuvant or maintenance therapy (National Comprehensive Cancer Network [NCCN]/European Society for Medical Oncology [ESMO]). Treatment with TMZ during and after radiotherapy was shown to increase median survival time by approximately 2.5 months compared to radiotherapy alone (14.6 months compared to 12.1 months) and increased 2-year survival rates by 17% (27% compared with 10%).[5] In the NCCN and ESMO guidelines, systemic chemotherapy is an option for those with recurrent disease; however, clinical trials are the recommended option (ESMO) over standard of care chemotherapeutics, including lomustine (NCCN). Furthermore, the 5-year survival rate of 9.8% in patients with GBM is still substantially less than that seen for other primary brain tumors.[6]

Unfortunately, despite many attempts to improve upon the available treatment options for those with GBM, there remains an urgent unmet need in this population because it has no adequate therapy and is almost universally fatal.[7] An emerging approach is to target the EGFR alterations present in 40% of glioblastoma using an antibody as a means to deliver cytotoxic compounds. A variety of antibody-drug conjugate constructs have been developed for this purpose, including toxins or antineoplastic agents and antibodies targeted to EGFR amplification or EGFRvIII mutants. The absence of EGFRvIII mutation and EGFR amplification in normal tissues makes this tumor-specific alteration an ideal candidate for such targeted approaches.

1.2 Epidermal Growth Factor Receptor-Amplified High-Grade Glioma in Children

High-grade glioma (HGG), defined as Grade III or IV glioma, has no adequate therapy and is almost universally fatal in both the adult and pediatric populations.[7]

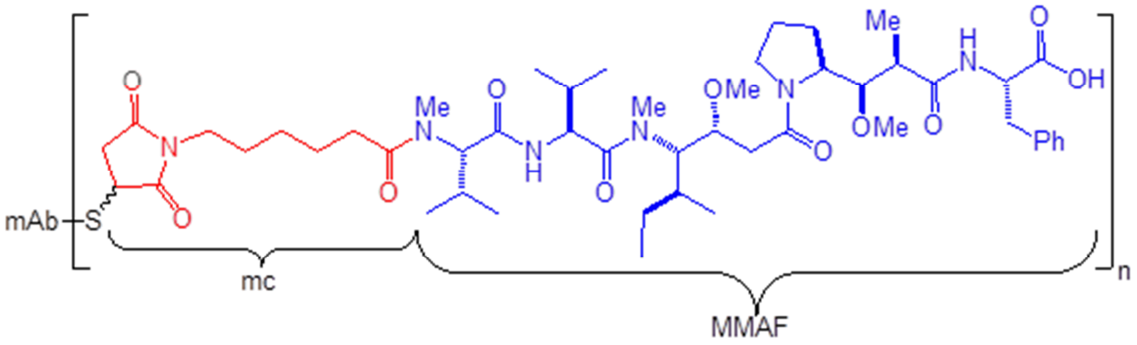
While the histology of glioma between adults and children appears identical, the biology of the tumors varies substantially. With respect to the genetic backgrounds, there are several differences between pediatric and adult glioma.[8,9] One of the most important gene-specific copy number alterations is EGFR amplification, which occurs in 40% of GBM tumors and has been shown to be a pivotal oncogenic driver in adult tumors. Multiple reports found in the literature demonstrate that EGFR amplification rates found in children with HGG are lower than in adult patients with GBM.[10-13] Using methods that are consistent with the assay used to determine eligibility in Study M14-483 (see Section 8.1.3), the rates in children with HGG were between 0% and 5%.

Pediatric HGG is a rare tumor with an annual incidence of approximately 0.85/100,000 persons/year according to the Central Brain Tumor Registry of the US.[14] The incidence rates for GBM, the most aggressive type of glioma, in the United States during 2004 through 2008 were 0.09 (0 to 4 years old), 0.14 (5 to 9 years old), 0.15 (10 to 14 years old), and 0.18 (15 to 19 years old) per 100,000 person-years.[15]

2.0 Mechanism of Action

ABT-414 is an antibody-drug conjugate comprised of the humanized chimeric anti-EGFR monoclonal antibody (mAb) ABT-806 conjugated via a stable maleimidocaproyl (mc) linker to a potent tubulin inhibitor, monomethylauristatin F (MMAF) (Figure 1). It binds to an epitope that is available predominantly on tumor cells with EGFRvIII or activated wild-type EGFR. The mAb component of ABT-414 delivers MMAF specifically to antigen-positive cells, where it disrupts the microtubule network, inducing cell cycle arrest and cell death.

Figure 1. Structure of ABT-414 Antibody-Drug Conjugate



Note: The maleimidocaproyl (mc) linker is shown in red, and the monomethylauristatin F (MMAF) drug is shown in blue; mAb is the ABT-806 antibody. A total of 2, 4, 6, or 8 mcMMAF molecules (n) can be conjugated to a single antibody.

3.0 Regulatory History

An investigational new drug (IND) application for ABT-414 for the treatment of solid tumors went into effect in July 2012. A clinical study specific to adults with GBM (Study M12-356) was initiated in the United States (US) in December 2012 and in the Netherlands in the European Union (EU) in February 2013. A total of 5 clinical trials in adults have been initiated in the US, EU, and other countries worldwide (see Section 5.0).

AbbVie Inc. (AbbVie) received orphan drug designation for ABT-414 in the US for GBM in May 2014 (14-4332) and in the EU for glioma on 29 July 2014 (EU/3/14/1305).

ABT-414 is being developed exclusively in GBM.

AbbVie intends to conduct a global pediatric program in the extremely rare indication of EGFR-amplified high-grade gliomas. Initial EU Paediatric Committee discussions were held in March 2015. AbbVie is actively evaluating clinical study designs, screening, and recruitment strategies that would allow execution of a pediatric study in the EU and US.

ABT-414 is not approved for marketing in the US or any other country worldwide.

4.0 Preclinical Data Supporting Clinical Studies

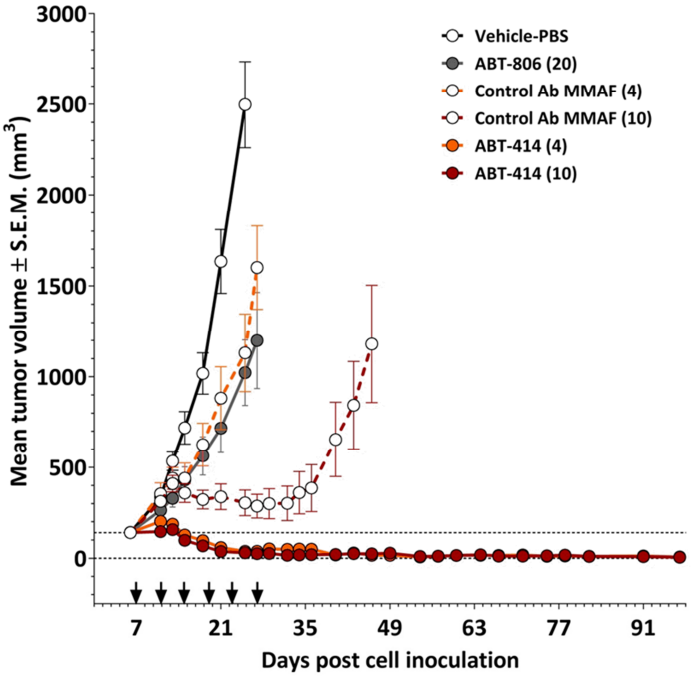
4.1 Primary Pharmacology

In vivo efficacy and selectivity of ABT-414 as monotherapy were evaluated in multiple murine xenograft models representing a variety of tumor types, including U87MGde2-7, a human GBM xenograft engineered to overexpress EGFRvIII. Tumor growth inhibition was proportional to the amount of ABT-414 administered, with maximal efficacy at doses of 3 or 4 mg/kg in several xenograft models, including U87MGde2-7. ABT-414 enhanced the efficacy of TMZ and radiation therapy (current standard of care for GBM and frequently used in pediatric HGG) in a murine U87MGde2-7 xenograft model.

4.1.1 ABT-414 Efficacy in EGFR-Amplified Glioblastoma Multiforme

ABT-414 induced complete regressions and cures at 4 mg/kg dosing in U87MGde2-7, a GBM-derived cell line engineered to express EGFRvIII (Figure 2). ABT-414 activity was also evaluated in the more clinically relevant GBM patient-derived xenograft (PDX) models. The SN0199 PDX model co-expressed amplified EGFR wild-type and EGFRvIII. ABT-414 had potent anti-tumor activity in this model, resulting in a significant overall survival advantage (Figure 3; Panel A). A second GBM PDX model (SN0207) expressing wild-type amplified EGFR was also evaluated, and responded well to ABT-414 treatment (Figure 3; Panel B).

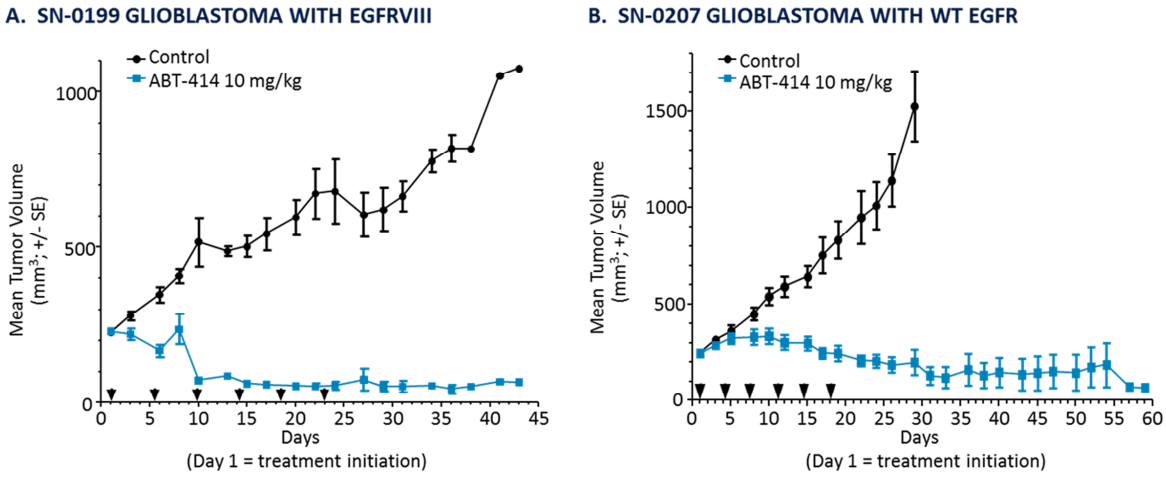
Figure 2. **In Vivo Activity of ABT-414 Against Glioblastoma Multiforme Tumors with EGFRvIII**



Ab = antibody; EGFRvIII = epidermal growth factor receptor mutant de2-7; MMAF = monomethylauristatin F; PBS = phosphate-buffered saline; S.E.M = standard error of measurement

The in vivo potency of ABT-414 was evaluated in mice implanted with U87MGde2-7. Due to the variable growth rate of the implanted patient-derived xenograft tumors, these studies were performed with an accrual design. Antibody-drug conjugates were administered every 4 days for a total of 6 doses at the doses indicated.

Figure 3. ABT-414 Monotherapy in Glioblastoma Multiforme Patient-Derived Xenograft Models with Amplified Epidermal Growth Factor Receptor

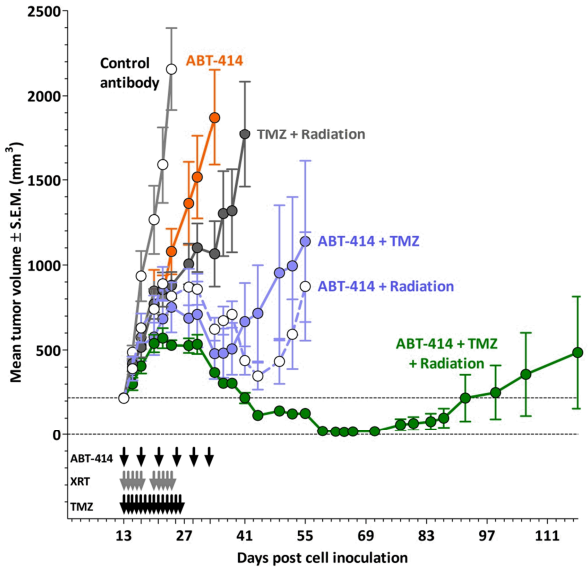


EGFR = epidermal growth factor receptor; EGFRvIII = epidermal growth factor receptor mutant de2-7; PDX = patient-derived xenograft; SE = standard error; WT = wild type

The in vivo potency of ABT-414 was evaluated in mice implanted with (A) PDX model SN-0199 and (B) PDX model SN-0207. Due to the variable growth rate of the implanted PDX tumors these studies were performed with an accrual design. Antibody-drug conjugates were administered every 4 days for a total of 6 doses at the doses indicated.

The ability to combine ABT-414 with standard of care chemotherapy was also evaluated in the U87MGde2-7 xenograft model. A dose of 1 mg/kg ABT-414 was used to permit assessment of its effect in combination with TMZ and radiation. Addition of ABT-414 to either TMZ or fractioned radiation therapy resulted in a significant increase in tumor growth inhibition. The triple combination displayed significant benefit over either double treatment supporting the potential of enhanced efficacy of this combination regimen (Figure 4).

Figure 4. ABT-414 in Combination with Temozolomide and Radiation

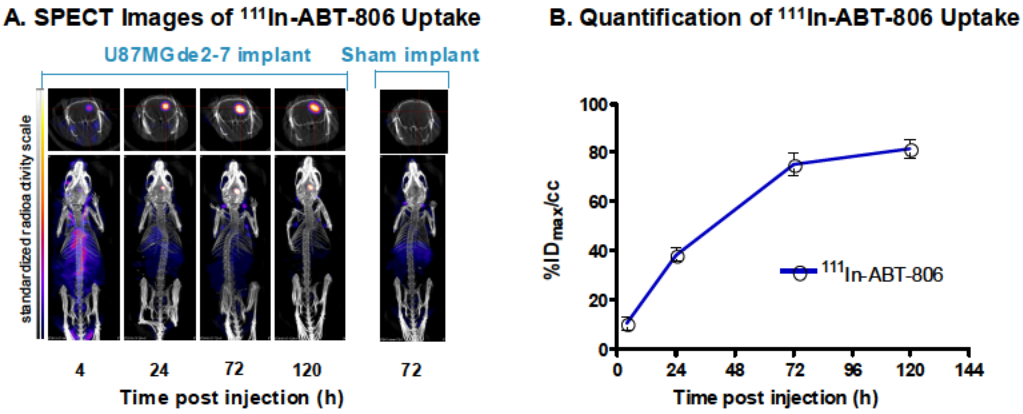


S.E.M = standard error of measurement; TMZ = temozolomide

ABT-414 significantly inhibited tumor growth when given every 4 days for a total of 6 doses. Addition of TMZ or radiation to ABT-414 increased the efficacy of ABT-414.

The blood brain barrier is a challenge to the use of antibody-drug conjugate therapy, potentially restricting access to tumors located within the brain. In order to evaluate the ability of ABT-414 to penetrate the blood brain barrier, mice were injected intracranially with U87MGde2-7 cells and following tumor development dosed intravenously with an indium labeled version of ABT-806 (^{111}In-ABT-806).[16] Tumor uptake was measured by single-photon emission computerized tomography/computerized tomography imaging and was observable at 4 hours, with maximal uptake at 120 hours post ^{111}In-ABT-806 dose. In contrast, there was no significant uptake of ^{111}In-ABT-806 in mice that received sham tumor implants (Figure 5). These results demonstrate efficient ^{111}In-ABT-806 uptake in this glioma model when grown orthotopically and is consistent with the utility of ABT-414 treatment in the GBM setting.

Figure 5. ABT-806i Tumor Uptake in Orthotopic Glioblastoma Multiforme Model in Combination with Temozolomide and Radiation



CT = computerized tomography; SPECT = single-photon emission computerized tomography
SPECT/CT images of mice bearing U87MGde2-7 intracranial tumors following injection of ^{111}In-ABT-806. (A) ^{111}In-ABT-806 tumor uptake is visible from 4 hours post injection, but not in animals with sham tumor implants. (B) Tumor uptake was quantified by SPECT/CT imaging and plotted as average tumor uptake (%IDmax/cc) against time.

4.2 Nonclinical Pharmacokinetics

ABT-414 pharmacokinetics was characterized following a single bolus intravenous dose in CD-1 mice, Sprague-Dawley rats, and cynomolgus monkeys. Additional studies characterized ABT-414 pharmacokinetics following once weekly dosing in CD-1 mice and cynomolgus monkeys (4 doses). In all studies, the ABT-414 pharmacokinetic profile was characteristic of a mAb, with low serum clearance values, very low steady-state volumes of distribution, and a terminal half-life of 8.0 to 9.5 days. Overall concentrations of ABT-806 mcMMAF (all antibody-drug conjugates with different drug loading ratios) were lower than those of total ABT-806 (unconjugated ABT-806 and ABT-806 mcMMAF combined), resulting in area under the concentration-time curve (AUC) values for ABT-806-mcMMAF that were approximately 40% to 50% lower than those of total ABT-806. Unconjugated cys-mcMMAF concentrations were very low following dosing with ABT-414, with both maximum observed plasma concentration (C_{max}) and AUC values more than 3 to 5 orders of magnitude lower than C_{max} and AUC of ABT-414.

Following repeated once weekly dosing in mice and monkeys, ABT-414 pharmacokinetics were characterized by dose-proportional increases in AUC, with values after the third dose being approximately 1.2- to 2.4-fold higher than those obtained after the first dose.

Cys-mcMMAF, identified as a metabolite of ABT-414, is eliminated through the hepatic biliary pathway and is a substrate of human P-glycoprotein (MDR-1). At concentrations up to 1 µM, cys-mcMMAF was not a direct, time- or metabolism-dependent inhibitor of cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 nor an inducer of CYP1A2, 2B6, or 3A/4/5 enzyme activity or gene expression and thus is unlikely to have drug-drug interaction in combination studies.

4.3 Nonclinical Toxicity and Development Plan

The toxicity profile of ABT-414 has been evaluated in adult animal studies of up to 3 months in duration. The primary findings observed with ABT-414 in toxicology studies are those that are considered potentially antigen mediated, MMAF related, or toxicities known to be observed with antibody-drug conjugates and other drugs that target EGFR. Adverse effects have been observed in skin and corneal epithelium; however, skin and corneal toxicity are well-known effects of EGFR-directed therapies and are not uncommon to antibody-drug conjugates in general.[17,18] Adverse effects in other tissues with rapidly dividing cells and reproductive organs have been observed. Because the mechanism of action of MMAF is microtubule disruption, adverse effects in these types of tissues are expected antigen-independent effects of ABT-414.[19,20]

All observed primary nonclinical toxicities are consistent with the pharmacology of ABT-414. Thus, in addition to the effects observed in the corneal epithelium of adult patients, toxicity to skin, tissues with rapidly dividing cells, or reproductive organs may be anticipated in pediatric patients administered ABT-414. Because toxicities based on ABT-414 pharmacology would also be expected in juvenile animals, and because both EGFR-directed therapies and microtubule toxins have a well-established toxicity profile in patients, potential toxicity in a pediatric population is considered sufficiently

characterized and a juvenile toxicity study in rodents would likely not provide any further characterization. Therefore, in accordance with ICH S9 guidance, AbbVie does not plan on conducting studies to assess the effects of ABT-414 in juvenile animals.

5.0 Clinical Trial Experience in Adults

5.1 Overview

ABT-414 is currently being assessed in 5 studies in adult patients, all of which are ongoing. These studies focus on patients with GBM.

- Study M12-356: Phase 1 (NCT 01800695)
- Study M13-379: Phase 1/2 (NCT 01741727)
- Study M13-714: Phase 1/2 (Japan)
- Study M14-483 (EORTC BTG-1410 or Intellance 2): Phase 2 (NCT 02343406)
- Study M13-813 (RTOG 3508 or Intellance 1): Phase 2b/3 (NCT 02573324)

5.2 Study M12-356

Study M12-356 is a Phase 1 open-label 3-arm study evaluating the safety and pharmacokinetics of ABT-414 in combination with radiation plus TMZ (Arm A), in combination with TMZ (Arm B), or as monotherapy (Arm C) in patients with GBM. Dose escalation has been completed for Arms A and B. Pharmacokinetic and safety data from all arms support recommended Phase 2 doses of 2.0 mg/kg for Arm A and 1.25 mg/kg for Arms B and C.[21]

As of April 2015, 19 patients have been treated in Arm B (0.5, 1.0, 1.25, and 1.5 mg/kg), and 27 patients have been treated in Arm C with 1.25 mg/kg ABT-414 every other week. Ten patients (53%) in Arm B and 17 patients (63%) in Arm C had EGFR amplification. The median study duration was 5.1 months for patients in Arm B and 2.2 months for patients in Arm C. Three patients in Arm B and 1 patient in Arm C achieved a complete response, as measured with the Revised Assessment in Neuro-Oncology (RANO) criteria.

In addition, 1 patient in each arm had a partial response. Of 27 patients in Arms B and C with EGFR amplification, 6 (22%) had confirmed responses ranging from 5 to 16 months in duration.[21]

As of April 2015, all patients in both arms had at least 1 adverse event. Common adverse events (≥ 40% in any arm) included eye disorders, blurred vision, foreign body sensation in the eyes, nausea, and fatigue. The most common Grade 3 or 4 adverse events were keratitis, γ-glutamyltransferase increase, convulsions, fatigue, and thrombocytopenia. Dose-limiting toxicities were corneal deposits and γ-glutamyltransferase increase in Arm B, and none were observed in Arm C.[21]

With the exception of ocular adverse events, described in more detail in Section 5.7, other adverse events were more likely related to the underlying cancer or concomitant chemotherapy or chemoradiotherapy.

The systemic exposures (C_{max} and AUC) of ABT-414, total ABT-806, and cys-mcMMAF achieved in patients after administration of ABT-414 via intravenous infusion were approximately dose proportional. The observed mean terminal half-lives of ABT-414, total ABT-806, and cys-mcMMAF were approximately 7, 9, and 4 days, respectively. There was no apparent pharmacokinetic interaction between ABT-414 and TMZ.

5.3 Study M13-379

Study M13-379 is a Phase 1/2 open-label study evaluating the safety, pharmacokinetics, and efficacy of ABT-414 in patients with advanced solid tumors likely to overexpress EGFR (Phase 1) and squamous non-small cell lung cancer (Phase 2). Dose escalation has been completed for Phase 1.

As of May 2015, 54 patients have received ABT-414 once every 3 weeks. A total of 13 patients (24%) had tumors with EGFR overexpression. The median number of previous lines of treatment was 3 (range, 1 to 7). The median duration of exposure to ABT-414 was 23 days (range, 2 to 217 days). After dose escalation, the recommended Phase 2 dose was set at 3 mg/kg once every 3 weeks.[22]

Response was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1. One partial response was observed in a patient with EGFR-amplified triple-negative breast cancer treated with the recommended Phase 2 dose. Stable disease occurred in 12 of 54 patients (22%), and the median duration of stable disease was 3.2 months.[22]

As of May 2015, 53 patients (98%) had at least 1 adverse event. The most common (≥ 40%) adverse events were blurred vision (most commonly due to transient microcystic keratopathy), fatigue, and nausea. The most common Grade 3/4 adverse events were keratitis, hyponatremia, blurred vision, dyspnea, and pneumonia. Eye pain was the only dose-limiting toxicity. The use of routine prophylactic steroid eye drops was implemented around the time of infusion at ABT-414 doses of 2.0 mg/kg or higher to reduce the severity of ocular toxicities and will be continued during the study.[22]

With the exception of ocular adverse events, described in more detail in Section 5.7, other adverse events were more likely related to the underlying cancer or concomitant chemotherapy or chemoradiotherapy.

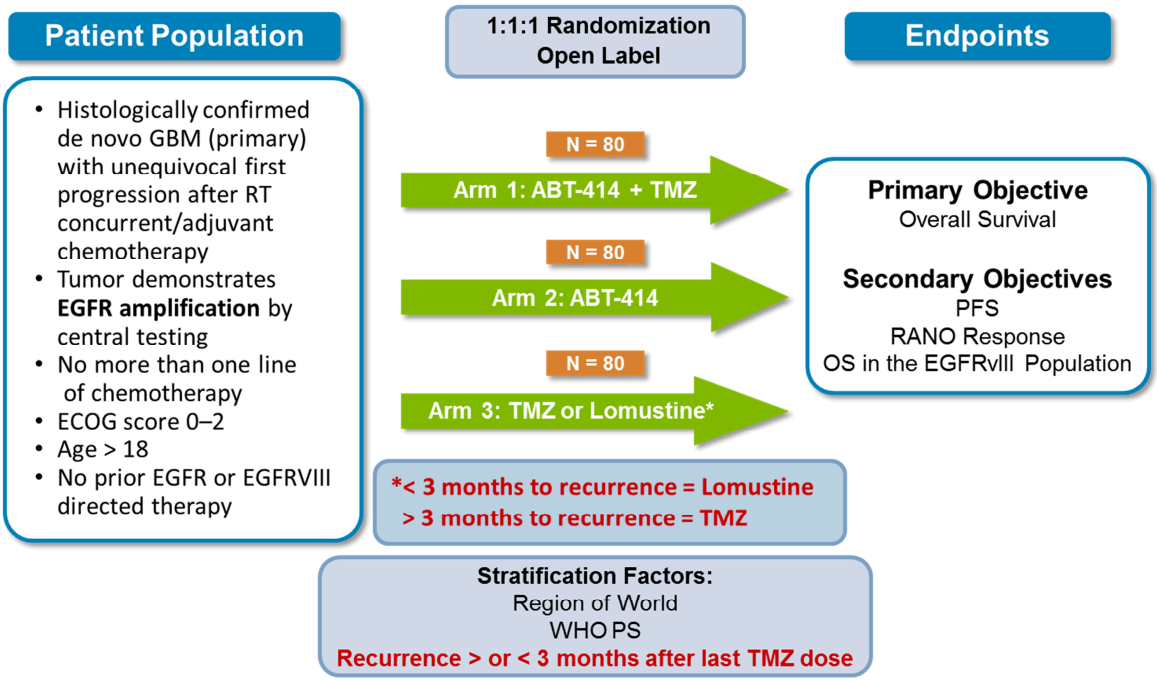
5.4 Study M13-714

Study M13-714 is a Phase 1/2 randomized, open-label, multicenter study evaluating the safety, pharmacokinetics, and efficacy of ABT-414 in Japanese adult patients with recurrent malignant glioma. In Phase 1, ABT-414 will be administered intravenously at 0.5 mg/kg up to 1.25 mg/kg every 2 weeks over 30 to 40 minutes in 12 to 18 patients with recurrent World Health Organization (WHO) Grade III or IV recurrent glioma. In Phase 2, ABT-414 will be administered intravenously at 1.25 mg/kg or the recommended Phase 2 dose to approximately 27 patients with recurrent GBM who have EGFR amplification. The primary endpoint in the Phase 2 portion is the progression-free survival rate at 6 months determined using RANO criteria. This study has been initiated and will be conducted in Japan.

5.5 Study M14-483 (EORTC BTG-1410, Intellance 2)

This study is being conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC). Study M14-483 (also known as EORTC BTG-1410 or Intellance 2) is a Phase 2 randomized open-label 3-arm study of ABT-414 in combination with TMZ (Arm 1), ABT-414 as monotherapy (Arm 2), lomustine (Arm 3A, for patients who relapse during TMZ treatment or within 16 weeks after the first day of the last TMZ cycle), or TMZ (Arm 3B, rechallenge for patients who relapse 16 weeks or more after the first day of the last dose of the TMZ cycle) in approximately 240 patients with recurrent EGFR amplified GBM. The study design is provided in Figure 6.

Figure 6. Study M14-483 Design



ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EGFRvIII = epidermal growth factor receptor mutant de2-7; GBM = glioblastoma multiforme; OS = overall survival; PFS = progression-free survival; PS = performance status; RT = radiotherapy; TMZ = temozolomide; WHO = World Health Organization

Patients in Arm 1 will be treated with 1.0 mg/kg ABT-414 administered as an intravenous infusion over 30 to 40 minutes once every 2 weeks in combination with 150 mg/m^2 TMZ on Days 1 through 5 for the first 28-day cycle with dose escalation to 200 mg/m^2 in subsequent cycles in case of good tolerance.

Patients in Arm 2 will be treated with 1.0 mg/kg ABT-414 administered as an intravenous infusion every 2 weeks over 30 to 40 minutes.

Patients in Arm 3A will be treated with 110 mg/m^2 lomustine on Day 1 of every 42-day treatment period for a maximum of 1 year. Patients in Arm 3B will be treated with 150 mg/m^2 TMZ on Days 1 through 5 for the first 28-day cycle with dose escalation to 200 mg/m^2 in subsequent cycles in case of good tolerance.

To achieve better tolerability to ocular toxicities, a 1.0 mg/kg ABT-414 dose was selected for Study M14-483 instead of the 1.25 mg/kg that was determined as the recommended Phase 2 dose from Arms B and C of Phase 1 Study M12-356. Tumor regression has also been observed at the 1.0 mg/kg dose of ABT-414 in Study M12-356.

Patients will be stratified according to the timing of the last cycle of TMZ to disease recurrence, region of the world, and WHO performance status. The primary endpoint is overall survival, with secondary endpoints of progression-free survival, progression-free survival at 6 months, and overall survival of the EGFRvIII subgroup. Response will be assessed according to RANO criteria. As of 01 October 2015, 9 patients have been randomized into Study M14-483.

5.6 Study M13-813 (RTOG 3508, Intellance 1)

This study is being conducted in collaboration with the Radiation Therapy Oncology Group (RTOG). Study M13-813 (also known as RTOG 3508 or Intellance 1) is a Phase 2b/3 randomized placebo-controlled study of ABT-414 with concurrent chemoradiation and adjuvant TMZ in approximately 720 patients with newly diagnosed GBM with EGFR amplification. Patients will receive ABT-414 or placebo during chemoradiation and adjuvant phases.

During the chemoradiation phase, ABT-414 will be administered at 2.0 mg/kg as an intravenous infusion over 30 to 40 minutes once every 2 weeks in addition to TMZ and radiotherapy.

The adjuvant phase will begin approximately 28 days after the last day of radiotherapy. ABT-414 will be administered at 1.25 mg/kg as an intravenous infusion on Days 1 and 15 of each 28-day cycle for 12 cycles in addition to TMZ.

The primary endpoint is overall survival for the overall study and progression-free survival for the Phase 2b portion.

5.7 Identified Risks

ABT-414 is composed of an EGFR-targeted antibody bound to a microtubule toxin, MMAF, which has been described to cause a unique and specific toxicity to the cornea: the formation of corneal epithelial microcysts. These microcysts are thought to be in reaction to damage caused by MMAF to the rapidly dividing transient amplifying cells that give rise to the cornea. When this damage occurs, these cells become necrotic and produce very small microcysts that become lodged in the early corneal layer. As the cornea regenerates, the microcysts traverse across the cornea, causing a variety of symptoms, and ultimately are sloughed off when a completely new cornea regenerates. This process can take 3 to 4 weeks, and thus, symptoms that arise may take at least 1 month before they start to improve. Adverse events associated with microcystic keratopathy have included dry eyes, blurred vision, eye pain, photophobia, and watery eyes.

Similar ophthalmologic toxicities to those observed with ABT-414 treatment have been previously reported with another MMAF-containing antibody-drug conjugate, SGN-75.[23] The ophthalmology examination findings with SGN-75, as well as with ABT-414, are similar to the findings noted with high-dose cytarabine administration.[24] Dose-limiting toxicities observed during the ABT-414 development program have generally been limited to ocular events secondary to microcystic keratopathy, and the events have been

reversible and dose dependent. Dexamethasone eye drops are commonly used with high-dose cytarabine administration to prevent the formation of epithelial microcysts. The steroid ophthalmic solution is thought to reduce the cellular turnover in the epithelium and thus make the cells more resistant to the effects of chemotherapy damage. Steroid eye drops are being used prophylactically with ABT-414 to help mitigate the ocular symptoms.

6.0 Other Clinical Trials that Are Ongoing or Completed

No other ABT-414 clinical trials sponsored by AbbVie or conducted in collaboration with partners are ongoing or have been completed at this time.

7.0 Current Drug Development Plan for Other Indications in Adults

Responses in patients with GBM enrolled in the ongoing Phase 1 clinical studies (Studies M12-356 and M13-379) have been restricted to patients whose tumors harbor EGFR gene amplification. Because EGFR amplification is an infrequent event outside of GBM, AbbVie is focusing further development of ABT-414 on patients with EGFR-amplified GBM. The safety profile of ABT-414 has been characterized in order to move into global Phase 2 studies in both front-line and recurrent GBM.

8.0 Proposed Pediatric Plan

The clinical strategy for the initial development of ABT-414 in the treatment of pediatric high-grade glioma (HGG) consists of opening a pediatric sub-study "nested" within the EORTC BTG-1410 (Study M14-483) randomized Phase 2 study of ABT-414 in adults with recurrent GBM.

8.1 Pediatric Sub-Study Nested Within the Phase 2 Randomized Study of ABT-414 in Adult Patients With Recurrent GBM (EORTC BTG-1410/M14-483)

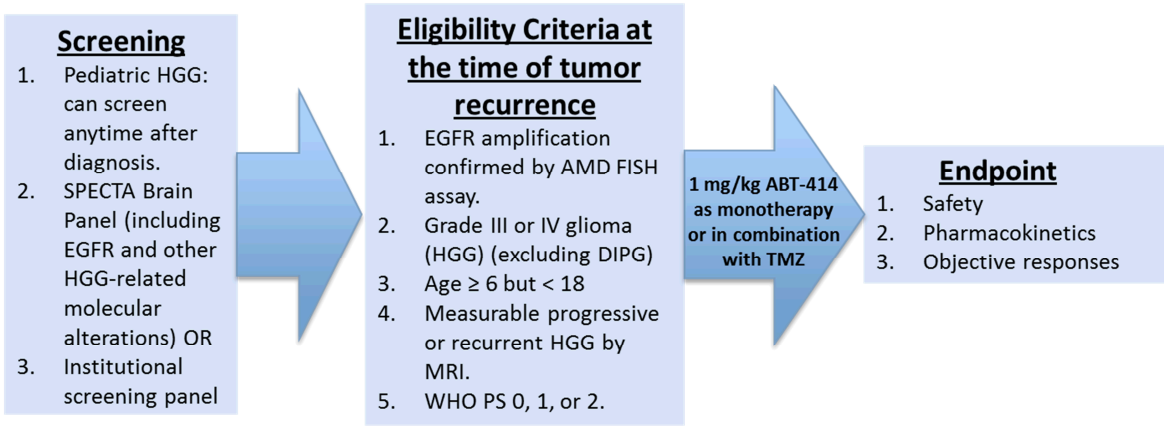
Pediatric HGG has an annual incidence of approximately 0.85/100,000 persons/year and EGFR amplification rate of 0% to 5% identified using methods that are consistent with the assay used to determine eligibility in Study M14-483.[11-14] Thus, based on expert advice provided by the Chairs of the High Grade Glioma Group of the Innovative Therapies for Children with Cancer (ITCC), EGFR amplification in pediatric HGG is considered to be too rare a condition to be studied in a stand-alone pediatric Phase 1/2 protocol. Therefore, AbbVie and the EORTC will write an amendment to the adult recurrent GBM study (EORTC BTG-1410/M14-483) with a pediatric-specific appendix outlining the eligibility (see Section 8.1.5, similar to the adult eligibility criteria), treatment plan, follow-up, and any other unique issues related to the pediatric population.

After particular consideration, AbbVie determined that pediatric patients will not be randomized to control comparators. Rather, all pediatric patients will receive 1.0 mg/kg ABT-414 (the recommended Phase 2 dose in adults) as monotherapy or in combination with TMZ. At the time of amendment approval, sites will add pediatric oncologists as sub-investigators, and the ITCC and other pediatric groups will be notified about the study. The adult study is summarized in Section 5.5, and the pediatric sub-study design is discussed below.

8.1.1 Objectives of the Pediatric Sub-Study

The primary objectives of the current proposed pediatric study will be to assess the safety profile and pharmacokinetics of ABT-414 monotherapy or in combination with TMZ in patients aged 6 to less than 18 who have EGFR-amplified recurrent HGG (Figure 7). Pediatric patients, unlike their adult counterparts, will all receive ABT-414 as either monotherapy or in combination with TMZ and will not be randomized to control comparators due to the rarity of EGFR-amplified pediatric HGG and the primary study objectives being safety and pharmacokinetics. Objective response will also be assessed.

Figure 7. Pediatric Sub-Study Nested Within Study M14-483



AMD = Abbott Molecular Diagnostics; DIPG = diffuse intrinsic pontine glioma; EGFR = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; HGG = high-grade glioma; MRI = magnetic resonance imaging; PS = performance status; SPECTA = Screening Patients for Efficient Clinical Trial Access; TMZ = temozolomide; WHO = World Health Organization

8.1.2 Investigators/Institutions

The investigators for the pediatric sub-study will be pediatric oncologists/ neuro-oncologists at the institutions where the adult study is currently open, as well as select additional children's hospitals as recommended by children's cancer cooperative groups, including the ITCC, Pediatric Brain Tumor Consortium, and Children's Oncology Group. Therefore, for the most part, the adult study and pediatric sub-study will be opened to recruit both adult and pediatric patients at the same institutions, but there may be additional children hospitals that will only participate in the pediatric sub-study. Study M14-483 is a global study, with countries in North America, Europe, and Asia all participating, and thus, AbbVie expects to include a wide range of children from all participating countries and institutions.

8.1.3 Study Population

The study population will include pediatric patients with HGG who have EGFR-amplified tumors greater than the chromosome 7 control. Patient tissue will be screened for EGFR

amplification using a next-generation, targeted DNA-seq panel (Screening Patients for Efficient Clinical Trial Access [SPECTA] brain), which consists of 600+ genes and includes most pediatric HGG genomic alterations (EGFR amplification included). Alternatively, pediatric patients with HGG may have tissue analyzed using similar platforms at their own institutions. Patients who screen positive for EGFR amplification will have follow-up validation testing done using the Abbott Molecular Diagnostic fluorescent in situ hybridization (FISH) assay, which is being developed as the companion diagnostic for ABT-414. Due to the rapidity of symptom progression at the time of recurrence, pediatric patients will be allowed to receive ABT-414 therapy once they screen positive for EGFR amplification but are awaiting the FISH assay confirmation.

8.1.4 Number of Patients to Be Enrolled

The sponsor plans to recruit at least 6 pediatric patients to enable evaluation of pharmacokinetics at the dose level of 1 mg/kg (see Section 8.1.6 for dosing). Based on a number of assumptions, including the past recruitment record of the ITCC, which conducted a Phase 1 study of EGFR targeted therapy in pediatric brain tumors of all histologies, AbbVie estimates the duration of patient recruitment for this study, which requires tissue screening and positivity for a molecular marker, is 3 years.

8.1.5 Main Inclusion and Exclusion Criteria

8.1.5.1 Inclusion Criteria

1. Patient must be between 6 to less than 18 years of age.
2. Patient must have a histologically proven WHO Grade III or IV glioma.
3. Confirmed EGFR amplification in patient's HGG tissue, either at diagnosis or at recurrence.
4. Patient must have recovered from the effects of surgery, postoperative infection, and other complications before Study Day 1 and have no significant post-operative hemorrhage.
5. Patient has a Karnofsky performance status of 70 or above.

6. Measurable tumor on magnetic resonance imaging with gadolinium.
7. Patient has adequate bone marrow, renal, and hepatic function as follows:
   a. Bone marrow: absolute neutrophil count ≥ 1,500/mm^3, platelets ≥ 100,000/mm^3; hemoglobin ≥ 9.0 g/dL (transfusion to achieve hemoglobin ≥ 9.0 g/dL is acceptable).
   b. Renal function: Serum creatinine ≤ 1.5 times the upper limit of the normal range.
   c. Hepatic function: Bilirubin < 1.5 times the upper limit of the normal range, and aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times the upper limit of the normal range. Prothrombin time/international normalized ratio ≤ 1.5. Patients on anticoagulant (such as Coumadin) will have prothrombin time and international normalized ratio as determined by the investigator.
8. Adolescent of child-bearing potential must agree to use adequate contraception prior to study entry, for the duration of study participation and for a period of 6 months following completion of therapy.

8.1.5.2 Main Exclusion Criteria

1. Patients with diffuse intrinsic pontine glioma.
2. Patient has received prior chemotherapy or radiotherapy for cancer of the head and neck region.
3. Patient has received anti-cancer therapy, including chemotherapy, immunotherapy, radiotherapy, hormonal, biologic, or any investigational therapy, within a period of 28 days prior to Study Day 1.
4. Patient has a history of major immunologic reaction to any immunoglobulin G-containing agent.
5. Patient has any medical condition which in the opinion of the investigator places the patient at an unacceptably high risk for toxicities.

6. Patient is a lactating or pregnant female.
7. Patient has had another active malignancy within the past 3 years except for any cancer considered cured.

8.1.6 Pediatric Dose Selection

Pharmacokinetic modeling and simulations using preliminary ABT-414 pharmacokinetic data from 161 adult patients with cancer in 2 Phase 1 studies indicate that body weight-based dosing provides similar ABT-414 pharmacokinetic exposure between adults and pediatric patients of ages 6 to 11 years and 12 to 17 years. Therefore, ABT-414 at 1 mg/kg, which is the current recommended dose for adult patients with recurrent GBM, with or without TMZ, will be administered to all pediatric patients with EGFR amplification every 2 weeks by intravenous infusion over 30 to 40 minutes. Each cycle will be defined as 28 days. There are no known risks to pediatric patients aged 6 to less than 18 years with the current intravenous formulation, which allows for accurate administration of the dose and does not include toxic excipients.

8.1.7 Methodology

Patients will visit the study site according to a pre-determined schedule as outlined in the study appendix/synopsis. All patients must have an ophthalmological examination at baseline, prior to initiation of ABT-414, and when clinically indicated after starting treatment. Patients may receive ABT-414 with or without TMZ as long as they continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for patient discontinuation. Temozolimide will be administered as per local prescribing guidelines and similar to the adult study. Routine prophylactic steroid eye drops will be used to reduce the severity of ocular toxicities.

8.1.8 Safety Assessment

Adverse events, laboratory profiles, physical exams, ophthalmological exams, electrocardiograms, and vital signs will be assessed throughout the study. All adverse

events will be entered into a dedicated pediatric database hosted by the EORTC. For patients who experience Grade III/IV ocular toxicity, a dose reduction schedule will be provided upon recovery.

8.1.9 Pharmacokinetic Assessment

Blood samples for the assay of ABT-414 and unconjugated cys-mcMMAF will be collected at designated time points after first infusion to determine the single-dose pharmacokinetics. Additional trough samples may be collected throughout the study. Blood samples will also be collected for the determination of anti-drug antibody.

8.1.10 Efficacy Assessment

Radiographic assessments for disease progression will be performed every other cycle (8 weeks) or as clinically indicated. Changes in measurable lesions over the course of therapy and changes in systemic steroid use and clinical status will be assessed using the RANO criteria. Survival information will be collected quarterly for all patients in the study and will continue until death or when the patients or legal guardians decide to withdraw from the study. If study drug discontinuation is indicated due to toxicity, patient decision, or treatment failure, a final visit will be conducted. All patients will have 1 follow-up visit approximately 35 days after the last dose of ABT-414 (5 times the half-life of ABT-414).

8.1.11 Criteria for Evaluation/Statistical Method

8.1.11.1 Safety

The worst grade of each adverse event item will be identified for each patient. Frequencies and percentages (whenever possible given the small number of patients) of each Common Terminology Criteria for Adverse Events term will be tabulated grouped by system organ class. The worst value of each hematological or biochemical category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated.

8.1.11.2 Efficacy

Objective response (determined using RANO criteria) will be described for each patient and will also be summarized as a rate (objective response rate). Other efficacy measures that will be reported descriptively for each patient and summarized as median include duration of overall response, time to response, progression-free survival, and overall survival.

Moreover, additional evaluation of clinical benefit will include Karnofsky performance status score change for the first 4 months on treatment, steroid dosage change, and change in frequency of seizures within the first 2 months on treatment.

Statistical considerations in evaluating efficacy in the pediatric subpopulation will be limited to an assessment of the above-mentioned endpoints using descriptive summaries. Inferential tests and specific statistical criteria cannot be set given the small number of patients expected to be enrolled despite the large screening effort planned.

8.1.11.3 Pharmacokinetic Analysis

Pharmacokinetic parameters of ABT-414 and cys-mcMMAF will be determined by noncompartmental methods. Individual pharmacokinetic parameters will be listed and summarized. The pediatric pharmacokinetic data may be analyzed with adult pharmacokinetic data from other studies in a nonlinear mixed effects modeling to estimate population pharmacokinetic parameters of ABT-414 and cys-mcMMAF, such as clearance and volume of distribution. The effect of demographic and/or disease-specific variable(s) on the pharmacokinetic parameters of ABT-414 and cys-mcMMAF will also be examined.

9.0 Current or Potential Challenges that Have Been Identified Regarding Clinical Trials in Children

The rarity of EGFR amplification in pediatric HGG leads to several problems that make a traditional clinical trial operationally infeasible. First, for every patient potentially eligible for a study, several study sites would have to be participating to capture that

patient in the catchment area of a participating site. Many potential sites are not interested in devoting the intensive resources needed for study start-up, given that in all likelihood, they will be unable to enroll any patients. Second, testing pediatric HGG tumors for EGFR amplification is not typically performed, potentially due to not only its rarity but also disappointing results with the EGFR inhibitor erlotinib in both adult and pediatric patients with HGG.[25]

Furthermore, the EGFR FISH assay AbbVie is developing with the ABT-414 program is not authorized for commercial use or use outside of a specific study setting, so the ability to conduct widespread screening to identify more eligible patients beyond the scope of the participating study sites is limited. Finally, gaining approval from sites to send tumor tissue for EGFR amplification testing by FISH, which measures only 1 genetic alteration and is unlikely to yield positive results, presents another challenge, as this is not the most efficient use of limited pediatric patient tumor tissue.

With these challenges in mind, AbbVie is proposing a nested pediatric study within Study M14-483/BTG-1410 due to the lack of other viable options. The nested study design was selected after a number of options were considered by AbbVie, including the following:

1. Stand-Alone Study: Pediatric cooperative groups, and in particular individual sites/investigators, stated that it would not be feasible to perform a pediatric stand-alone study. A stand-alone study would require substantial resources and efforts by each participating institution in order to initiate and participate in a study with a very high screen failure rate. Conversely, adding a pediatric sub-investigator to an ongoing adult study would be significantly less burdensome to the site, given the relatively low likelihood of identifying appropriate patients with EGFR-amplified tumors.
2. All-Comer HGG Study: A study in children who have non-EGFR-amplified HGG, could expose children to treatment-emergent toxicities with no evidence to suggest potential for clinical benefit at this time. Given the results presented earlier in this

document, the adult research program has limited enrollment to only those patients with EGFR-amplified disease, and a similar strategy is recommended for pediatric development.

3. AbbVie-Sponsored Screening Program for EGFR Amplification: Although this could facilitate referrals for a stand-alone study or the nested study, it would still require substantial efforts from sites and willingness to contribute tumor tissues despite a very low yield of patients with EGFR-amplified tumors.

The nested study takes advantage of the existing arrangements with study sites participating in the ABT-414 adult GBM program, including some sites where services for pediatric and adult glioma co-exist. AbbVie will continue to explore participation of large US institutions that currently treat pediatric patients with HGG. In addition, AbbVie proposes to broaden screening efforts by funding external molecular screening programs (including SPECTA) that include testing for EGFR amplification as a service to patients. Patients with EGFR-amplified tumors will be notified that they may be eligible for a clinical trial and provided with referral materials if they are interested. However, patients will receive the same molecular screening profile results usually provided by these programs, and AbbVie's funding of such broad screening will in no way be contingent on the patient's willingness to participate in the ABT-414 study.

10.0 Summary

In summary, ABT-414 has demonstrated promising activity in adults with glioblastoma – a devastating disease with few treatment options. High-grade gliomas are equally devastating in the pediatric population; therefore, it is critical to explore all potential avenues to provide ABT-414 treatment for children. This nested study proposal provides a commitment to develop ABT-414 in a very uncommon pediatric tumor, and presents a unique solution to the challenge of developing a drug in a rare condition.

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